

## Review Article

# A Comprehensive Review on the Therapeutic Effects of *Salvia hispanica* L. (Chia) on Metabolic Dysfunction–Associated Fatty Liver Disease: Special Focus on Pathogenesis

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Metabolic dysfunction–associated fatty liver disease (MAFLD) is the most common chronic liver condition with a bidirectional relation with multimetabolic disorders. By considering lifestyle interventions as the approved treatment strategy, several herbal products have been examined as conjugated therapy in the prevention/treatment of the disease. The annual herbaceous plant known as *Salvia hispanica* L. (chia) is an ancient grain trending in modern diets. Chia seeds are not only an excellent source of nutrients and bioactive compounds but also have shown effectiveness in the management of a number of metabolic disorders. However, studies on MAFLD are limited and mainly include animal models. Moreover, the exact molecular mechanisms by which chia influences MAFLD-related outcomes remain inadequately investigated. Hence, the aim of the present comprehensive review is to explore the effectiveness of chia supplementation in MAFLD by various forms (seeds, oil, and flour) with a view point on molecular pathways, metabolic regulation, and clinical outcomes.

**Keywords:** chia; metabolic dysfunction–associated fatty liver disease; obesity; *Salvia hispanica* L

## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a liver disorder described by the accumulation of triglycerides (TGs) more than 5%–10% of the liver weight in the absence of etiologies, such as alcohol abuse, medications, and viral hepatitis [1–5]. To date, scientific societies have moved toward a novel nomenclature as metabolic dysfunction–associated fatty liver disease (MAFLD). The diagnosis of MAFLD is based on the presence of hepatic steatosis in addition to at least one of the following criteria: Type 2 diabetes mellitus (T2DM),

obesity, or evidence of metabolic dysregulation. Recent studies have demonstrated that MAFLD serves as an independent risk factor for atherosclerosis and shows a stronger correlation with major cardiometabolic risk factors, including dyslipidemia, T2DM, and hypertension, and thereby offers a more accurate representation of the disease's systemic impact, compared with NAFLD [6–10]. Currently, the pooled prevalence of MAFLD has been estimated to be 39.22% [11]. MAFLD is considered the most common chronic liver disorder, and lifestyle modification (including dietary interventions and physical activity)

remains the first-line treatment strategy; meanwhile, standardized dietary guidelines are still lacking. A balanced diet with personalized approaches (calorie restriction, high-protein, low-carbohydrate) is recommended. More precisely, increased intake of whole grains, plant-based proteins, low-fat dairy, healthy oils, and fruits/vegetables, beside reduced intake of processed meats, ultra-processed foods, and added sugars, are recommended. Following specific dietary approaches such as Mediterranean diet and regular exercise further support the management of MAFLD [12]. MAFLD encompasses a broad range of diseases, from simple steatosis to fibrosis, cirrhosis, and hepatocellular cancer [13–16]. The pathogenic roots of MAFLD are explained by the “multiple-hits theory” representing the interplay among numerous hepatic and extrahepatic complications [17–19]. MAFLD involves genetic factors and an excessive accumulation of fatty tissue, accompanied by insulin resistance (IR), dysbiosis of the intestinal microbiome, proinflammatory markers, and oxidative stress, all of which exacerbate the condition [20–23]. In this regard, supplementation with omega-3 fatty acids and chia seeds as compounds rich in  $\alpha$ -linolenic acid (ALA) and fiber has gained significant attention in the treatment of MAFLD and related metabolic conditions [24, 25].

Chia seed (*Salvia hispanica* L.) is an annual herbaceous plant belonging to the *Lamiaceae* family that grows in southern Mexico and northern Guatemala, as well as tropical and subtropical mountainous regions [24]. The species reaches a height of almost 1 m. Chia seed has a smooth and shiny black or white surface and is composed of approximately 486 Kcal per 100 g, 16% protein, 30% fat, 34% fiber, and 42% carbohydrate, respectively [26]. The seed contains high concentrations of proteins (mainly prolamins, glutamines, globulins, and albumins) as well as essential amino acids (i.e., isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, histidine, and valine). Glutamine is identified as the major amino acid, and histidine has the lowest concentration in the mentioned amino acid profile of chia seed [27, 28]. Regarding the micronutrient content of chia, the seed is comprised of various vitamins (A, B1, B2, B3, C, and E) and minerals (calcium, magnesium, iron, phosphorus, zinc, manganese, potassium, and sodium) as well as being a major plant reservoir of omega-3 fatty acids, ALA, and fiber (insoluble and soluble). In addition, chia seeds are potent sources of polyphenols, carotenoids, anthocyanins, and various types of active antioxidative compounds such as phenolic acids, flavonoids, chlorogenic acid, caffeic acid, myristic acid, quercetin, kaempferol, besides polyunsaturated fatty acids (PUFAs) [24, 29, 30].

The efficacy of chia seed in enhancing the function and mobility of the digestive system and the proliferation of enterocytes has led to its widespread use in the food, cosmetic, health, and pharmaceutical industries [31]. Moreover, recent evidence highlights the cardio- and hepatoprotective properties of chia seed, which exert antiatherosclerotic, anti-inflammatory, and antioxidative activities in different clinical conditions [31]. Chia seed is recognized for its antidiabetic and antiseptic properties, with its anticonstipation effect being the most specific mechanism of action [31].

Taken together, chia has been examined in a variety of diseases by exerting several therapeutic properties as a functional, novel, and healthy food [25, 32, 33]. Despite the accumulating evidence on the application of chia in metabolic disorders, studies on MAFLD are limited and mainly include animal models. In addition, there is a lack of research on the precise molecular processes of chia's effects on outcomes associated with MAFLD [25, 32, 33]. Therefore, the present comprehensive review aims to investigate the potential mechanistic effects of *Salvia hispanica* L. (chia) supplementation on MAFLD by providing insight into the main pathological pathways involved in the presence and progression of fatty liver disease.

## 2. Methods

Study findings were reviewed subsequent to a comprehensive search in the online databases, such as PubMed, Scopus, Google Scholar, and Web of Science, until 2024. The literature search aimed to address the studies investigating the effects of *Salvia hispanica* L. (chia) on MAFLD and its metabolic components using medical subject heading terms (MeSH) and non-MeSH terms. In vitro, animal, and human studies were considered eligible to be included. Included studies and related extracted data were classified based on pathogenic hits of MAFLD, including obesity, IR, oxidative stress, inflammation, gut microbiome, metabolic regulation, and liver function. Characteristics of the mentioned studies are represented in Table 1.

## 3. The Effect of Chia Supplementation on the Hits of MAFLD

**3.1. Obesity.** Adipocyte expansion is a potential player in the presence and development of MAFLD [21]. More precisely, abnormal and excessive accumulation of fatty substrates throughout the adipose tissue is closely correlated with the progression of hepatic steatosis via direct and indirect drivers. In this context, substantial evidence has underscored the two-way relationship between overweight/obesity and MAFLD [21, 34]. Obesity leads to the deterioration of the pathological conditions involved in the progression of MAFLD, including microbiome dysbiosis, hormonal imbalance, and the activation of proinflammatory/oxidative signaling pathways [21, 35, 36]. In this context, several treatment strategies have targeted body weight to facilitate the development of MAFLD [20–22]. Calorie restriction, low-carbohydrate diets, appetite suppressants, and glucose-lowering medications are common strategies to reestablish a healthy energy balance as the leading conventional therapy for obesity [37–39].

In the past decade, chia seed has gained significant attention from researchers based on its high fiber content and bioactive compounds [40]. The antiobesity features of chia supplementation have been examined in different chronic conditions, such as T2DM, MAFLD, hypertension, dyslipidemia, and metabolic syndrome [38]. Ferreira et al. [41] studied male Wistar rats using control ( $n = 24$ ) and experimental ( $n = 48$ ) groups. Wistar rats were given a sucrose-

TABLE 1: General characteristics of studies included.

| Studies                   | Study design                | Study population                                                        | Dose and duration                                                       | Risk factors                                                                             | Findings                                                                                                                                                                                    |
|---------------------------|-----------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Obesity</i>            |                             |                                                                         |                                                                         |                                                                                          |                                                                                                                                                                                             |
| Carnier et al. [38]       | Animal                      | 52 male mice                                                            | Chia flour 12 g/kg of food<br>10 weeks                                  | Adipose tissue, glycemic profile                                                         | Increase in n-3 PUFAs in epididymal adipose tissue and prevention and treatment of obesity<br>Reduction in fat mass, dyslipidemia, and insulin resistance and increase in glucose tolerance |
| Ferreira et al. [41]      | Animal                      | 72 male C57BL/6 mice                                                    | Chia seeds 362 g/kg diet<br>3–6 months                                  | Body composition and insulin signaling                                                   | Improvement in morphology associated with lower lipid deposit in hepatocytes and increase in intestinal muscle layers and crypt size                                                        |
| Chani et al. [42]         | Animal                      | 20 male Sprague Dawley rats                                             | Chia seed 10% chia seeds 10 and 13 months                               | Body measurements, musculoskeletal system, the liver, and the intestines                 | Increase in intakes of dietary fiber and reduction in intake of food, hyperglycemia in T2DM, the risk of diet-related diseases such as CVD, Type 2 diabetes, and some cancers               |
| Chon et al. [44]          | Randomized controlled trial | 15 overweight/obese women                                               | Chia seeds 41 g/day (10% of total energy intake) 8 weeks                | Dietary displacement                                                                     | Reduction in AMPK activity and senescence markers in epididymal adipose tissue                                                                                                              |
| Rui et al. [46]           | Animal                      | 32 mouse-prone 8 (SAMP8)                                                | Chia seed powder 10 g dissolved in 100 g high-fat diets (HFDs) 18 weeks | Senescence markers in epididymal adipose tissue                                          | Improvement in insulin sensitivity and plasma lipid profile reduction in body fat                                                                                                           |
| Oliva et al. [40]         | Animal                      | 42 male Wistar rats                                                     | Chia seed 362 g/kg of diet 3 months                                     | Body fat and modulates adipocyte lipid                                                   | Decrease in lipid accumulation and increase in mitochondrial fatty acid oxidation                                                                                                           |
| Pandurangan et al. [45]   | In vitro                    | Human mesenchymal stem cells (hMSCs)                                    | Chia seed fatty acid extract 0.2, 0.4 µg/mL 14 days                     | Adipocyte's fatty acid accumulation and maturation                                       | Improvement in insulin resistance and liver damage associated with MAFLD                                                                                                                    |
| Maturana et al. [37]      | Animal                      | 18 males C57BL/6J mice                                                  | Black and white chia leaf ethanolic extract 50 mg/kg/day 12 weeks       | Biochemical and hepatic markers                                                          |                                                                                                                                                                                             |
| <i>Insulin resistance</i> |                             |                                                                         |                                                                         |                                                                                          |                                                                                                                                                                                             |
| Rossi et al. [59]         | Animal                      | 48 male Wistar rats                                                     | Chia seed 362 g/kg diet 5 months                                        | Hepatic transcription factors and their target lipogenic and oxidative enzyme activities | Reduction in postprandial glucose excursion and improvement in dyslipidemia and liver steatosis                                                                                             |
| Fonte-Faria et al. [52]   | Animal                      | 16 male C57BL/6 mice                                                    | Chia oil (0.15%) 90–135 days                                            | Body composition and insulin signaling                                                   | Increase in glucose tolerance and reduction in fat mass accumulation and increase in lean mass                                                                                              |
| Alamri et al. [54]        | Animal                      | 40 adult male albino Sprague Dawley rats: Nondiabetic and diabetic rats | Chia seeds: 20% of white 20% of black 6 weeks                           | Physiological parameters                                                                 | Reduction in the levels of fasting blood glucose and improvement in lipid profile and liver function                                                                                        |

TABLE 1: Continued.

| Studies                 | Study design                | Study population                                                    | Dose and duration                                                    | Risk factors                                                     | Findings                                                                                                                                                         |
|-------------------------|-----------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Enes et al. [49]        | In vivo and in vitro        | 40 Wistar rats                                                      | Flour and oil chia—chia flour (14.7%) and chia oil (4%) 10 weeks     | Glucose metabolism                                               | Improvement in glucose tolerance and decrease in adiposity                                                                                                       |
| Ferreira et al. [56]    | Animal                      | 42 male Wistar rats                                                 | Chia seed 362 g/kg of diet 6 months                                  | Skeletal muscle lipotoxicity and insulin resistance              | Increase in lipid content in the skeletal muscle                                                                                                                 |
| Mihafu et al. [57]      | Animal                      | 20 male Wistar rats                                                 | Chia seed extract 20 g 28 days                                       | Postprandial glycemia, body weight, and hematological parameters | Reduction in postprandial glycemia and improvement in hematological parameters                                                                                   |
| Sosa-Crespo et al. [50] | Randomized controlled trial | 9 patients (insulin resistance or T2D)                              | Chia seed 50 mg/kg 2 weeks                                           | Blood glucose, plasma insulin, and Matsuda–DeFronzo index        | No significant effect on plasmatic insulin                                                                                                                       |
| Trisnadi et al. [55]    | Animal                      | 15 male Wistar rats with diabetes                                   | Chia seed extract 4.5 mg/kg BW and 13.5 mg/KgBW 7 days               | Blood sugar levels                                               | Reduction in blood sugar                                                                                                                                         |
| <i>Oxidative stress</i> |                             |                                                                     |                                                                      |                                                                  |                                                                                                                                                                  |
| Silva et al. [65]       | Animal                      | 36 Wistar rats                                                      | Chia seed and oil 13.3% of chia seed 4% of chia oil 12 weeks         | Plasma and liver oxidative status                                | Improvement in antioxidant defense system                                                                                                                        |
| Mohamed et al. [68]     | Animal                      | 24 male Sprague Dawley rats                                         | Chia seeds oil 300 mg/kg BW 1 month                                  | Oxidative stress, inflammation, and dyslipidemia                 | Reduction in inflammatory markers and oxidative stress, and improvement in dyslipidemia                                                                          |
| <i>Inflammation</i>     |                             |                                                                     |                                                                      |                                                                  |                                                                                                                                                                  |
| Da Silva et al. [65]    | Animal                      | 32 male rats ( <i>Rattus norvegicus</i> , Wistar albinus variation) | Chia flour based on 50% of the recommended amount of calcium 35 days | Calcium bioavailability and inflammation                         | Reduction in inflammatory processes and improvement in the lipid profile and no effect on oxidative stress                                                       |
| <i>Gut microbiome</i>   |                             |                                                                     |                                                                      |                                                                  |                                                                                                                                                                  |
| Tamargo et al. [80]     | In vitro                    | Dynamic gastrointestinal model                                      | Chia seed mucilage (0.3%, 0.5% and 0.8%) 8 days                      | Human gut microbiota                                             | No effect on the physical properties of the intestine (viscosity of the lumen) and effective on bacterial growth and metabolic activity of intestinal microbiota |

TABLE 1: Continued.

| Studies                     | Study design            | Study population            | Dose and duration                                                     | Risk factors                                                                               | Findings                                                                                                                                |
|-----------------------------|-------------------------|-----------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Silva et al. [65]           | In vivo                 | 105 chicks                  | Soluble extracts from chia seed 5, 10, 25, 50 mg/mL 17 days           | Brush border membrane functionality, morphology, and intestinal bacterial populations      | Improvement in intestinal health and intestinal mineral absorption                                                                      |
| Mishima et al. [78]         | Animal                  | 32 male Wistar rats         | Chia seed 40 g of chia/day 35 days                                    | Intestinal health                                                                          | Improvement in intestinal morphology and functionality                                                                                  |
| <i>Metabolic regulation</i> |                         |                             |                                                                       |                                                                                            |                                                                                                                                         |
| Mishima et al. [78]         | Animal                  | 80 female Wistar rats       | Chia flour based on 20% of the recommended amount of calcium 18 weeks | Biometric measurements, oxidative stress, mineral content, and ATPase enzymes in the heart | Improvement in antioxidant activity and reduction in the heart fat content                                                              |
| Dias Moreira et al. [82]    | Animal                  | 40 Wistar rats              | Chia flour and oil 14.7% of CF, 4% of CO 8,10 weeks                   | Metabolic disorders                                                                        | Improvement in lipogenesis, blood glucose, TG levels, and body weight and reduction in liver inflammation and degree of liver steatosis |
| <i>Liver function</i>       |                         |                             |                                                                       |                                                                                            |                                                                                                                                         |
| Han et al. [30]             | Animal                  | 60 male Kunming mice rats   | Chia oil 950 mg kg/bw, 1900 mg kg/bw 8 weeks                          | Hyperlipidemia and oxidative stress                                                        | Reduction in hepatic steatosis, lipid deposition in the liver, hyperlipidemia, and oxidative stress                                     |
| Medina-Urrutia et al. [24]  | Single-arm experimental | 25 NAFLD patients           | Chia flour 25 g/day 8 weeks                                           | NAFLD and metabolic abnormalities                                                          | Improvement in NAFLD and metabolic abnormalities                                                                                        |
| Poudyal et al. [89]         | Animal                  | 48 male Wistar rats         | Chia seeds 5% added to food 8 weeks                                   | Metabolic, cardiovascular, and hepatic                                                     | Decrease in hepatic steatosis and cardiac and hepatic inflammation                                                                      |
| Aras et al. [82]            | Animal                  | 49 Sprague Dawley male rats | Chia oil 1 mL/kg 14 days                                              | Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) and interleukin 6 (IL-6)                  | Decrease in blood glucose                                                                                                               |

rich diet for 3 months. Then, half of the animals kept using a sucrose-rich diet until month six, while in the other half, corn oil was replaced by chia seeds for 3 months (sucrose-rich diet + chia). A reference group consistently consumed a control diet. The study found potential benefits of dietary chia seed intervention on adipose tissue oxidative stress and adipose tissue malfunction, which a sucrose-rich diet causes.

In another study, Chani et al. [42] investigated the effects of chia seeds on body measures, liver and gut, and the musculoskeletal system of 20 male Sprague Dawley rats. Rats were divided into two groups: one group was fed a diet containing 10% chia seeds, while the other group received a conventional isocaloric diet for 10 and 13 months. Consequently, assessing specific body parameters illustrated changes in bone mineral content based on densitometry analysis and gut and hepatic morphology. These findings favored chia seed supplementation over a conventional diet.

The primary mechanism of action for chia's weight-lowering activity appears to be its high dietary fiber content and its impact on satiety [43]. Hence, chia not only suppresses appetite but also its fiber content improves insulin sensitivity by delaying gastric emptying, which also attenuates postprandial blood glucose levels [44]. Specifically, soluble fiber enhances glucose and lipid homeostasis by decreasing postprandial glucose responses to carbohydrate consumption. Reduced levels of low-density lipoprotein cholesterol (LDL-c) are caused by increasing LDL-c receptors and stopping the absorption of bile and cholesterol, which leads to changes that lower blood cholesterol levels [44]. Moreover, dietary fiber facilitates beneficial alterations in hormone secretion, enhancing satiety and promoting anti-inflammatory effects [44].

Another mechanistic effect is attributed to the fatty acid content of chia as a 3:1 ratio of omega 3 to omega 6 fatty acids, thereby exerting immunoregulatory and antiobesity characteristics. This ratio inhibits adipocyte lipogenesis and hypertrophy, which simultaneously mitigates the production/secretion of proinflammatory cytokines in adipose tissue and inhibits adipocyte maturation and lipid accumulation [45]. Notably, the fatty acid content and chia seed ratio could effectively target several molecular signatures involved in mitochondria-dependent fatty acid  $\beta$ -oxidation and lipolysis. 5'-Adenosine monophosphate-activated protein kinase (AMPK) is one of the hallmark molecules involved in the mentioned functions. It has been elucidated that chia seed could increase the levels of phosphorylated AMPK, reducing the senescence markers of adipose tissue, regulating fatty acid  $\beta$ -oxidation, and inhibiting TG accumulation through its downstream signaling pathways [46]. Accordingly, following AMPK activation, upregulation of uncoupling protein-1, peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) coactivator 1 alpha, sterol regulatory element binding protein-1c (SREBP-1c), and PR domain containing 16 contribute to adipocyte mitochondrial  $\beta$ -oxidation and stimulate mitochondrial thermogenesis in mature adipocytes, following chia seed intervention [45]. These findings were strengthened by a study that documented the ability of chia seed extract and

its fatty acid compartments to inhibit PPAR $\gamma$  and CCAAT/enhancer binding protein activity, leading to the significant suppression of adipocyte hyperplasia [45]. Triggering the mentioned molecular signature by chia seed intervention finally emerges as stimulated mitochondrial  $\beta$ -oxidation, depleted TG storages, and an evident lipid-lowering effect, even in blood or visceral tissues.

The fatty acid content of chia seed is associated with the downregulation of mRNA related to adipocyte hyperplasia, which leads to increased expression of genes involved in mitochondrial fatty acid oxidation and a subsequent decrease in lipid deposition [45].

Far from the fatty acid profile, rosmarinic acid—a derivative of hydroxycinnamic acid and caffeic acid—has recently been detected and measured in ethanolic extracts of chia leaves. Findings have noticed the effect of these compounds in contracting with lipid accumulation via promoting lipolysis and downregulating adipogenic factors in human adipocytes [37]. Polyphenols are compounds that exhibit beneficial effects on the adipocyte-hepatic axis through various mechanisms, including antioxidant activities (by regulating antioxidant enzyme activity), metabolic activities (by reducing lipogenesis), and anti-inflammatory effects (by modulating proinflammatory cytokines) [37].

As illustrated in Figure 1, chia seeds and their leaves could exert weight-lowering effects by modulating several mechanistic pathways that trigger appetite sensation, fatty acid  $\beta$ -oxidation, glucose and lipid homeostasis, and oxidative stress, mainly through their specific ingredients. However, due to the studies' limitations, the mentioned pathways should be open to further investigation in human randomized clinical trials.

**3.2. IR.** IR—the failed response to insulin by cells—is a predominant pathological hit in the occurrence and development of MAFLD [47, 48]. IR is characterized by the condition in which cells cannot use insulin, or the pancreas cannot produce enough hormone, resulting in high blood glucose [49]. Genetic and epigenetic factors, adipocyte expansion and dysfunction, and disturbances in adipocyte-derived hormones all contribute to this pathological state. These factors inhibit myocyte glycogenesis and stimulate lipolysis, facilitating the influx of glucose and lipids into the hepatic axis [47]. Hyperinsulinemia is another consequence of IR linked to MAFLD through the stimulation of *de novo* lipogenesis and storage of lipid droplets in liver parenchyma [47]. IR serves as a central pathogenic factor in the progression of various metabolic diseases, including T2DM, metabolic syndrome, obesity, and MAFLD, establishing connections among them [12]. Different treatment strategies (dietary interventions and synthetic/herbal supplements) have targeted IR in metabolic diseases, and the AMPK/phosphoinositol-3-kinase/protein kinase-B (AKT) pathway is predominantly involved in this context [22, 50, 51].

As mentioned, chia (*Salvia hispanica*) is a great source of ALA, protein, dietary fiber, minerals, vitamins, phenolic compounds, and free fatty acids that could be useful in maintaining blood sugar levels [22]. Several animal studies and clinical trials have examined the favorable properties of



FIGURE 1: Mechanistic actions of chia in the management of obesity and hyperglycemia. MAFLD, nonalcoholic fatty liver disease; FBS, fasting blood sugar; IRS-1, insulin receptor substrate 1; PPAR, peroxisome proliferator-activated receptor; GLUT4, glucose transporter type 4; IR, insulin resistance; AMPK, adenosine monophosphate-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor γ; UCP-1, upregulation of uncoupling protein-1 (UCP-1); PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; SREBP-1c, sterol regulatory element binding protein-1c (SREBP-1c).

chia (seeds or oil) on insulin function. For example, in the survey by Fonte-Faria et al. [52], male C57BL/6 mice ( $n = 8$  per group) were fed with regular control chow or a high-fat diet (HFD) for 135 days. Another group of mice was fed with HFD plus chia oil from 90 to 135 days. Compared to other groups, the obese rats in this experimental group exhibited improved glucose tolerance and insulin sensitivity. The underlying molecular mechanism was associated with an increase in insulin receptor substrate-1 tyrosine phosphorylation, AKT phosphorylation, and translocation of the glucose transporter-4 to the plasma membrane in the gastrocnemius muscle after insulin stimulation. Indeed, another animal model by Nery Enesa et al. [49] investigated the effects of chia flour and oil on Wistar rats by exploring glucose metabolism. Animals received a standard diet, HFD, and high-fat and high-fructose diet (HFHF) for 8 weeks, and then, the HFHF group was divided into three groups receiving either chia flour (HFHF plus 14.7% of chia flour) or chia oil (HFHF plus 4% of chia oil). It was documented that chia oil and flour could enhance glucose and insulin tolerance via increasing AKT phosphorylation and glycolysis in rats fed with an HFHF diet, plus chia flour and oil, which also reduces adiposity. Their results also underscored the potential impact of chia on glucose metabolism through insulin-independent mechanisms, including AMPK modulation. These findings have also been validated in numerous clinical trials for patients with T2DM, and they have been observed to significantly improve glucose homeostasis,

appetite, and body weight [50, 53, 54]. For example, Fernandez et al. [53], in a randomized clinical trial, examined the effects of chia seeds as an adjuvant treatment for T2DM and reported significant increases in adiponectin levels and a subsequent decrease in fasting blood glucose and lipids such as total cholesterol and LDL-c as well as waist circumference. An animal study by Husna et al. [36] in 2019 demonstrated the effects of chia seed extraction plus moderate exercise on hyperglycemia in T2DM. Their results illuminated the effectiveness of chia seeds on the upregulation of hepatic AMPK, which increased glucose absorption, oxidation, and regulated glycolytic enzymes [50, 55]. With this regard, chia oil and flour could enhance glucose and insulin tolerance via increasing AKT phosphorylation, enhancing glycolysis, and reducing adipocyte accumulation by activating AMPK [49]. Far from chia seeds, findings suggest that ALA, a bioactive compound in chia oil, mediates insulin and glucose resistance. Chia oil supplements stimulate insulin cell signaling pathways and decrease the proportion of body fat, thereby restoring the hepatocyte's energy fuel system in animal models with obesity [52]. These changes have been attributed to the positive correlation between improved glycemic response and the percentage of body lean mass, which has been referred to as increased glucose uptake sites [49, 52, 56]. A cell line study on HepG2 insulin-resistant cells encompassed the modulatory effect of hydrolyzed phenolic extract of chia on gluconeogenic and glycolytic enzyme gene expression levels [49].

Another mechanism of action has been attributed to the soluble fiber component of chia, which enhances the intestinal lumen's viscosity and thereby directly decreases the absorption of glucose by eliminating intestinal food transit time and the interaction between glucose and enterocytes [54]. Its dietary fiber also shows positive effects on postponing gastric emptying, emerged as lower postprandial blood glucose concentrations, and enhanced insulin sensitivity [54]. This evidence was also associated with the translocation of the glucose transporter-4 to the plasma membrane [52].

The fatty acid content of chia is not only involved in its weight-lowering properties but has also been examined in experimental studies in IR conditions. These studies shed light on the efficacy of black and white chia seeds on the attenuation of postprandial glycemia [54, 57]. Ferreira et al. [56] demonstrated that dietary supplementation with chia seeds increased the incorporation of ALA and docosapentaenoic acid (DHA) in phospholipids of rats by IR. In this line, higher levels of dietary ALA were linked to improved insulin function and dyslipidemia and diminished risk of IR. Following chia supplementation, its omega-3 PUFAs incorporate into the fraction of phospholipids in the lipid membrane of adipocytes [54, 57, 58]. These changes emerge as increased membrane fluidity improves insulin action. In addition, ALA phosphorylates protein AS160 and activates AMPK, which is involved in glucose homeostasis, increases the absorption of glucose in an insulin-dependent manner, and eliminates blood glucose levels [55].

High ALA contents of chia seeds also trigger mRNA expression levels of PPARs. In this context, chia seeds increase the protein levels of PPAR $\alpha$  and, hence, decrease the accumulation of hepatic TG by overactivating carnitine palmitoyltransferase-1 and fatty acid oxidase enzymes [59]. Evidence also suggests the ability of chia seed intervention to upregulate PPAR $\gamma$  levels and consequently regulate the expression of genes involved in lipid metabolism and insulin signaling, such as PPAR $\gamma$  coactivator-1  $\alpha$  and lipoprotein lipase [60, 61]. Furthermore, PPAR $\gamma$  overexpression improves glucose uptake and interacts with IR [55, 56].

Figure 1 also represents that chia supplementation in forms like seeds and even oil could target specific signatures such as PPARs and potentially improve insulin signaling and its downstream molecular pathway (specifically AMPK/PI3K/AKT pathway) through its fatty acid content and at the same time target gastrointestinal tract to improve glucose absorption. The exact mechanism of insulin-sensitive action on human and animal models of MAFLD is unclear, necessitating further investigation by assessing glucose profile and IR-related indices in well-designed clinical trials.

**3.3. Oxidative Stress.** Oxidative stress is defined by the imbalance between the production of free radicals and the body's protective endogenous antioxidant systems [62, 63]. A proinflammatory state is developed as the first result of oxidative stress, which lowers antioxidant capacity and increases the production of free radicals [62]. Excessive levels of reactive oxygen species (ROS) can also damage cells' DNA, lipids, and proteins, leading to cellular death or dysfunction [62, 64]. The

present mechanisms are attributed to the pathogenesis of MAFLD in a synergistic manner [62]. The current knowledge demonstrates that consuming natural products with antioxidative bioactive components inhibits oxidative stress and offers a natural substitute for treating and preventing chronic disorders. Here, functional foods reduce ROS and improve the efficacy of antioxidant systems. Far from well-known and applied vitamins, minerals, and fatty acids, chia seed has received great attention due to its antioxidative properties in recent decades. As a botanical source of ALA, chia is rich in flavonoids and polyphenols with high antioxidative activities followed by anti-inflammatory properties [65–67].

More precisely, chia seed and oil, known as natural antioxidants, consist of high concentrations of tocopherols, phytosterols, carotenoids, and phenolic compounds that exert potent antioxidative activity and inhibit oxidative stress through improving antioxidant defense and reducing lipid peroxidation in animal models [65]. Daily consumption of chia seed oil provides a source of omega-3 fatty acids with a 3:1 ratio of ALA (64%) to linoleic acid (21%), respectively [68]. Silva Marinelli et al. [65] examined the influence of chia seeds and oil on diet-induced obesity in rats. They reported fine-tuned plasma antioxidant status, which emerged as reductions in glutathione levels and increases in catalase and glutathione peroxidase activity, which improved the liver and plasma oxidative state and relieved plasma lipid peroxidation. Mohamed et al. [68] enriched chia seed oil with dietary fibers (mucilage) and phytosterol as a novel nutritional supplement to protect the heart against oxidative stress, inflammation, and dyslipidemia. Their findings suggested that chia produced the least amount of superoxide dismutase protein production and decreased thiobarbituric acid reactive substances, but not a reduction in its activity [69]. Another experimental study on rats on a high-fructose diet highlighted the ability of chia to reverse the balance between free radical generation and antioxidative defense, thereby increasing the susceptibility of lipids to peroxidation. These changes affected oxidative stress regarding improvements in glutathione levels and hepatic antioxidant enzyme activity, including catalase, superoxide dismutase, and glutathione peroxidase [65].

The fundamental processes by which chia mitigates the production of ROS or exhibits direct scavenging capabilities pertain to its capacity to transform into active molecules that diminish cellular damage and facilitate signaling transduction and gene expression in molecular contexts [29]. Chia seeds contain significant quantities of ALA and antioxidant compounds that stimulate nuclear factor erythroid 2-related factor 2 and manganese superoxide dismutase, which counteract with pro-oxidative state and improve ROS levels and lipid peroxidation [62]. Although a decrease in pro-oxidative chemicals or an increase in antioxidant compounds is an existing theory, the main mechanisms are still unclear, and further research is required [62, 65].

**3.4. Inflammation.** Evidence increasingly indicates that chronic low-grade inflammation plays a central role in the progression of multiple metabolic disorders [70]. With this regard, obesity and adipokine secretion stimulate the

production of proinflammatory cytokines and facilitate the activation of inflammatory cascades, which in turn aggravate hepatic function and lead to the progression of simple steatosis to more severe pathologies in the spectrum of MAFLD [70, 71]. Chia is a rich source of proteins, peptides, and omega-3 PUFAs with possible anti-inflammatory and antioxidative properties [72]. Almost 20% of the chia seed is comprised of proteins, including albumin, glutelin, and other protein fractions that specifically trigger inflammation, oxidative stress, atherosclerosis, and adipogenesis [73].

In vitro findings on digested chia proteins and peptides revealed their ability to prevent and inhibit the activation of inflammatory pathways by blocking PPAR $\gamma$  and its downstream transcriptional factors, such as nuclear factor kappa-B (NF- $\kappa$ B) [74]. The mentioned genes also regulate adipogenesis and inhibit adipocyte expansion, alleviating inflammation [74]. Indeed, total protein (as the combination of all protein fractions) and especially glutelin significantly fine-tuned adipogenesis and inflammation, suggesting that glutelin is the primary driver of anti-inflammatory aspects of chia [74]. Silva et al. [75] investigated the benefits of chia consumption on calcium absorption, lipid profile, oxidative stress, and inflammatory status in young Wistar rats following a standard diet, HFD, and a typical Western diet focusing on calcium bioavailability. Regardless of the type of prescribed diet, chia consumption exerted a positive impact on tumor necrosis factor- $\alpha$  (TNF $\alpha$ )-related inflammatory pathway and lipid profile while failing to affect oxidative stress.

According to the findings, chia's immunomodulatory and anti-inflammatory properties (specifically chia oil) have been attributed to its high ALA concentrations, inhibiting oxidative processes and suppressing the production of proinflammatory cytokines in peripheral blood mononuclear cells. At the same time, ALA exerts anti-inflammatory features by mitigating proinflammatory signaling pathways and downregulating the gene expression levels of inducible nitric oxide synthase as an oxidative-inflammatory mediator, cyclooxygenase-2, and TNF $\alpha$  gene expressions. These changes are evident through mitogen-activated protein kinase and NF- $\kappa$ B inhibition in lipopolysaccharide-induced murine macrophage cells. [72]. High PUFA concentrations in Chia, by itself, could regulate the expression levels of NF- $\kappa$ B and PPARs, thereby reducing mRNA expression levels of interleukin-6 and TNF- $\alpha$  as proinflammatory adipokines. These changes also result in improvements in insulin sensitivity in skeletal muscle [38].

As mentioned, chia seed's omega-6 to omega-3 fatty acid ratio is predominant in its therapeutic potency by underpowering metabolic and oxidative events. Likewise, the fatty acid ratio suppresses adipocyte lipogenesis and hypertrophy, which promotes the suppression of proinflammatory cytokine generation in adipose tissue [38].

Figure 2 represents the alternative mechanistic actions of chia on metabolic, oxidative-inflammatory, and gut-related consequences of MAFLD. It should be mentioned that chia intervention exerts metabolic-regulatory properties following the diminished production of proinflammatory cytokines and free radicals (Figure 2). However, a complete viewpoint must be achieved by assessing proinflammatory

and anti-inflammatory mediators simultaneously in different models of MAFLD.

**3.5. Gut Microbiome.** Robust evidence has focused on and highlighted the potential role of chia seed in intestinal health. Chia, a rich source of dietary fiber and bioactive substances, is a viable dietary ingredient that improves intestinal composition function and mineral absorption [41]. As introduced earlier, gut microbiota plays a pivotal role in developing MAFLD. In conjunction with the immunological and entero-endocrine systems, gut microbiota establishes a complex network that regulates the function of the intestinal barrier. Additionally, studies have shown that bacteria-derived metabolites and the balance in gut microbiota are crucial for controlling the various metabolic processes in the body [20, 76, 77]. Herewith, gut microbiome dysbiosis is closely correlated with an unhealthy diet and its components. In particular, plants contain nondigestible dietary fiber and bioactive compounds that affect intestinal bacterial population, gastrointestinal motility, functionality, and morphology and increase mucus production, goblet cell number as well as villi surface area, and crypt depth [78, 79].

Another experimental study aimed to determine how young Wistar rats' intestinal function was affected by chia prescription. Thirty-six Wistar rats were divided into six groups (6 animals each): the control group was fed the American Institute of Nutrition-93M diet; the HFF group was fed an HFHFD; the chia seed short (6-wk) and long (12-wk) treatments received an HFF diet with chia seed; chia oil short (6-wk) and long (12-wk) treatments received an HFF diet with chia oil. This study investigates the intestinal alterations in young Wistar rats subjected to an HFD following chia intervention, revealing notable enhancements in intestinal function, morphology, the circular muscle layer, and fecal moisture content. The most remarkable outcome was the enhanced short-chain fatty acid (SCFA) production following chia supplementation. This finding pointed out that chia positively affects the microorganisms that produce SCFAs, such as butyric acid, acetic acid, and propionic acid, as the most abundant fecal metabolites. These fermentation products could reduce intestinal pH and improve mineral absorption and solubility [78]. Besides serving as the primary energy source for colonocytes, butyric acid enhances intestinal epithelial cells' integrity by improving tight junctions and cell proliferation [20]. Indeed, acetic acid and propionic acid could promote anti-inflammatory processes and cytokine production. Acetic acid is the most abundant SCFA and plays a significant regulatory role in body weight control and insulin sensitivity, serving as a direct mediator in lipid metabolism and glucose homeostasis [78].

The effects of chia seed mucilage on human gut microbiota have been studied by Alba Tamargo et al. [80]. This study illuminated that chia mucilage could affect gut microbiota's bacterial growth and metabolic activity without affecting lumen viscosity. Results showed differences in viscosities between mucilage concentrations before chia feeding and in the first stage of the dig, and chia mucilage may impact the growth of bacteria and metabolic activity of intestinal microbiota. Still, it does not affect the viscosity of the lumen.

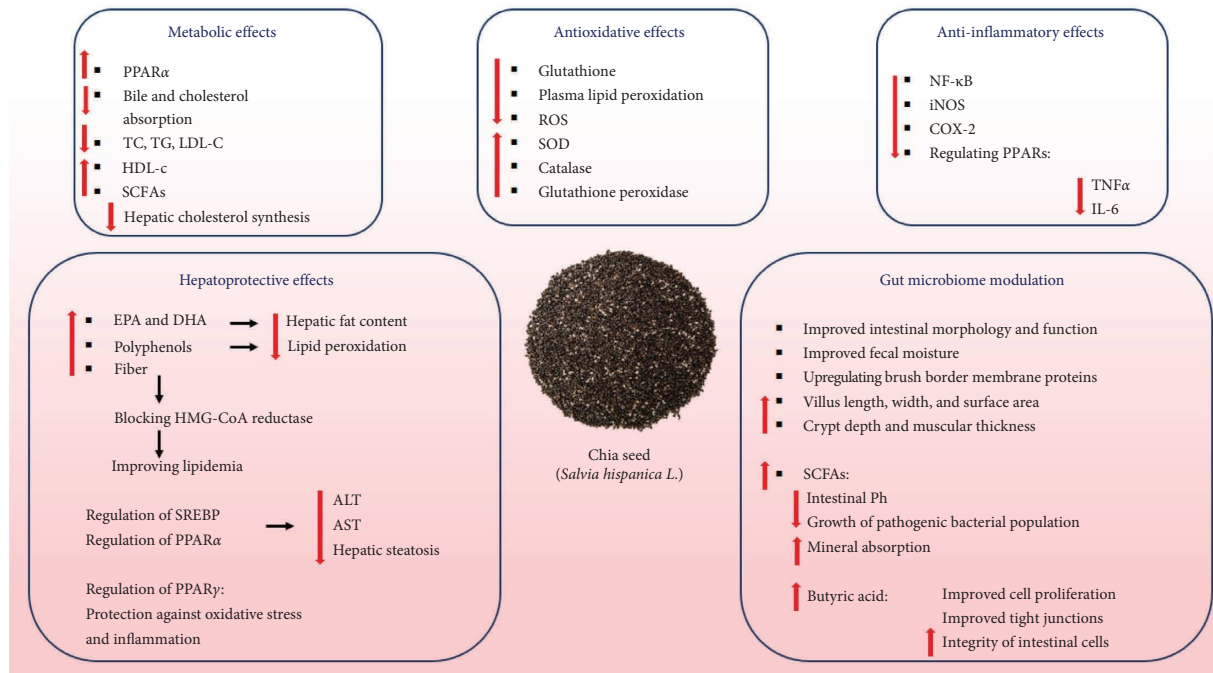


FIGURE 2: Mechanistic actions of chia in the management of metabolic, oxidative-inflammatory, and gut-related consequences of MAFLD. PPARα, peroxisome proliferator-activated receptor α; TC, total cholesterol; TG, triglyceride; LDL cholesterol, low-density lipoprotein cholesterol; HDL cholesterol, high-density lipoprotein cholesterol; SCFAs, short-chain fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPARγ, peroxisome proliferator-activated receptor γ; SREBP, sterol regulatory element binding; SOD, superoxide dismutase; ROS, radical oxygen species; TNF-α, tumor necrosis factor; NF-κB, nuclear factor kappa β; PPAR, peroxisome proliferator-activated receptor; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; iNOS, inducible nitric oxide synthetase; COX-2, cyclooxygenase-2.

As of yet, recent studies have documented the effectiveness of soluble extracts from chia on macro- and micronutrients' absorption and digestion through upregulating the genes related to brush border membrane proteins. Additionally, the intestinal pH is decreased by the bacterial production of SCFAs and the intestinal fermentation of dietary fiber following the consumption of chia. It increases the solubility and absorption of minerals by inhibiting the proliferation of potentially pathogenic bacterial populations. The production of SCFAs also promotes the proliferation of epithelial cells, which enhances the absorptive surface area and aids in the absorption of dietary minerals [79].

By considering other forms of administration, chia soluble extracts increased all parameters related to intestinal villi (villus surface area, villus length, and width) (Figure 2) [79]. Adding strength to the present findings, rosmarinic acid and rosmarinyl glucoside are two phenolic compounds highly concentrated in the soluble extract of chia seeds that affect intestinal morphology by increasing the villus height, crypt depth, and muscular thickness [78–80]. Hence, there is a consensus on the ability of chia seeds and chia extracts as herbal-origin soluble extracts with high fiber content to exert prebiotic properties.

**3.6. Metabolic Regulation.** MAFLD—the barometer of metabolic health—is co-incident with several metabolic disturbances like dyslipidemia, metabolic syndrome, and endocrine disorders. As MAFLD is the liver component of

the mentioned entities, specialists have suggested MAFLD to define the pathology and underlying risk factors better [21]. Hence, planning a comprehensive treatment strategy to face MAFLD-related risk factors seems necessary [81]. Functional foods and/or their isolated bioactive components have been efficient in the treatment of MAFLD and the risk of developing metabolic liver diseases [22]. From this viewpoint, chia seeds are distinguished by their functionality, evidenced by their dietary fiber, proteins, lipids (predominantly ALA), vitamins, minerals, and bioactive substances [82].

Several studies have focused on the metabolic-regulatory properties of chia in different forms. For example, consumption of both black and white chia seeds effectively reduced total cholesterol, TG, and LDL-c in an animal model [38]. According to Pandurangan et al. [45], the lipid-lowering properties of chia seed may be related to increased levels of uncoupling protein-1, PPARC1, PRDM16, and adiponectin. These factors stimulate mitochondrial oxidation and lead to the depletion of TG storage. These findings were also approved when chia flour or oil was added to an imbalanced diet rich in saturated fat and fructose, as it reduced metabolic disorders by modulating different mechanisms to improve liver health [82].

Different forms and dosages of chia could improve lipid profile by increasing the levels of ALA, eicosapentaenoic acid (EPA), and other omega-3 fatty acids [83]. Providing ALA increases the availability of n-3 PUFA substrates, which

modulate the activity of key enzymes ( $\Delta$ -6 desaturase,  $\Delta$ -5 desaturase, and Elov12) that preferentially metabolize n-3 PUFAs. This leads to an upregulation of PUFA synthesis, primarily in the liver. Thus, ALA availability plays a crucial role in modulating n-3 PUFA production [84]. In addition, increased tissue levels of n-3 long-chain PUFAs such as EPA and DHA result in a negative feedback mechanism that regulates the activity and expression of  $\Delta$ 5- and  $\Delta$ 6-desaturase enzymes involved in long-chain PUFA biosynthesis. Concurrently, ALA enhances the expression and DNA-binding activity of the transcription factor PPAR- $\alpha$ , which promotes fatty acid  $\beta$ -oxidation, while suppressing SREBP-1c, a key regulator of lipogenesis. These molecular effects lead to reduced lipogenic enzyme activities, metabolic regulation in terms of lipid homeostasis, and improved antioxidant status in the liver and adipose tissue [85, 86]. Fiber contents of chia lead to an increase in LDL-c receptor activation and inhibit the absorption of bile and cholesterol, resulting in reduced plasma levels of LDL-c [44]. In addition, the soluble fiber in chia seed is responsible for rapid food transit time and slow digestion but is also fermented by the large intestine bacteria and produces SCFAs [68]. In turn, the absorption of SCFAs mitigates the hepatic cholesterol biosynthetic ability and reduces blood cholesterol levels, besides increasing the excretion of bile acids due to acidification of the colon environment [68]. Furthermore, chia flour and oil could restore the antioxidant system and increase fatty acid oxidation. In this regard, chia oil specifically improved TG levels and body weight, while chia flour modulated lipogenesis. These changes also emerged as alleviations in the severity of hepatic steatosis [82]. Meanwhile, further research on other aspects of metabolic pathways is required.

**3.7. Liver Function.** MAFLD is characterized by mild to moderately elevated serum levels of aminotransferases, including aspartate transaminase (AST) and alanine transaminase (ALT) [87, 88]. Previous studies focused on MAFLD-related pathological conditions and documented the favorable effects of chia. However, reducing aminotransferases and hepatic steatosis remains the first-line treatment step for MAFLD [87, 88]. To date, knowledge of chia supplementation at various pharmacological doses (20–40 g per day) has demonstrated positive hepatoprotective effects in animal models. Redistribution of serum lipids, reductions in hepatic lipid accumulation, and visceral tissue lipid content have been observed after chia intervention [24].

An investigation on co-supplementation with dandelion extract plus chia oil on the liver tissues of diabetic rats demonstrated that long-term use of chia in the diet decreases lipid accumulation in the liver [88]. In line with them, Han et al. [30] investigated the effects of chia seed oil on oxidative stress and hyperlipidemia in HFD-fed mice. Their findings demonstrated improvements in hepatic steatosis. Another animal model approved these findings by administering chia seed oil and chia flour and assessing the liver of Wistar rats fed with an HFHFD. Their findings highlighted the

cardioprotective features of chia and its ability to alleviate the degree of hepatic steatosis independently by improving inflammatory markers [82]. Medina-Urrutia et al. [24] evaluated the effects of a diet supplemented with ground chia (25 g/day for 8 weeks) on 25 patients with previous MAFLD diagnosis and suggested that milled chia could ameliorate MAFLD and prevent the appearance of metabolic consequences as well as advanced stages of MAFLD due to its composition. Additionally, Poudyal et al. [89] assessed hepatic and cardiometabolic effects of 5% chia seed supplementation on rats fed with a high-carbohydrate, HFD with low n-3 fatty acids and reported an increase in the activity of ALT and a decrease in the activity of AST and creatine kinase. Diets of the treatment groups were supplemented with 5% chia seeds after 8 weeks on the H diet for a further 8 weeks. Compared with the H rats, they reported an increase in the activity of ALT as well as a decrease in AST and creatine kinase activity after consuming chia [49].

To understand the related mechanisms, it should be noted that chia derivatives, such as hydroxycinnamic acid, increase lipolysis and suppress the storage of fat. However, these findings must be approved in patients with MAFLD [24]. The hepatoprotective mechanisms of chia seeds are illustrated in Figure 2. In this context, chia is also high in omega-3 fatty acids, affecting liver function. More precisely, high EPA and DHA concentrations can also reduce intrahepatic fat content and improve the metabolic profile of individuals with MAFLD [54]. Additionally, the polyphenols, caffeic acid, and chlorogenic acid in chia seeds could reduce lipid peroxidation and positively affect the liver through antioxidant and anti-inflammatory activity [54, 90]. Chia seeds' mucilage also contains soluble, sticky fibers that reduce cholesterol by blocking 3-hydroxy 3-methylglutaryl coenzyme reductase and increasing the excretion of bile acids [54, 90]. Hence, it is evident that chia consumption results in considerable increases in serum HDL-c and decreases in cholesterol and TG content that subsequently improve liver status [54]. Chia seed and its ALA and phenolic components modulate the expression of nuclear receptors such as SREBP-1C, PPAR- $\alpha$ , and carnitine palmitoyltransferase-1 and then regulate *de novo* lipogenesis, beta-oxidation, and redox system as the main mechanisms contributing to the improvement of MAFLD [54, 90].

Regarding the specific changes in PPAR expression, PPAR- $\alpha$  and PPAR- $\gamma$  are regulated by chia supplementation. Namely, high concentrations of PPAR- $\alpha$  act as a regulator for lipid metabolism and free fatty acid oxidation and attenuate the p65 NF- $\kappa$ B-related proinflammatory state and hepatic steatosis. PPAR- $\alpha$  activation consequently mitigates MAFLD by reducing liver enzyme levels (AST and ALT) and uric acid levels as a marker of liver injury [54, 90]. Hepatic expression of PPAR- $\gamma$  and nuclear factor erythroid-2 is mediated by chia to protect against ROS generation in MAFLD [90].

## 4. Strengths and Limitations

This comprehensive review has some limitations. Included studies administered chia in different forms. The protein,

fiber, fat, vitamins, and mineral content of chia depend on various factors such as genetics and growth environmental conditions, which might differ among the mentioned studies. Most of the studies utilized a small sample size. However, this study had some strengths such as prioritizing the studies focusing on different chia sources and their distinct mechanistic effects, and highlighting the activated and suppressed molecular signaling pathways following chia intervention in different study designs. Taken together, despite the limited evidence regarding chia supplementation in the context of MAFLD in various study designs, a number of preclinical and small-scale clinical studies suggest that a daily intake of 25 to 40 g of chia over a period of 6 to 12 weeks may exert favorable effects on hepatic steatosis, IR, dyslipidemia, and inflammation. However, the heterogeneity among study designs, intervention duration, and dosage should be considered. The present review emphasizes the need for well-controlled, large-scale clinical trials to determine the optimal dose, duration, and clinical efficacy of chia supplementation in the management of MAFLD.

## 5. Conclusion

In conclusion, chia (*Salvia hispanica* L.) as an herbaceous plant exerts potent metabolic-regulating features and improves glycemic control, lipid profile, oxidative state, and body fatty acid levels in different forms (seeds, flour, and oil) and dosages. Meanwhile, further well-designed studies are required to elucidate the exact role of chia as a dietary supplement in patients with MAFLD.

## Nomenclature

|             |                                                      |
|-------------|------------------------------------------------------|
| Akt         | Protein kinase-B                                     |
| ALA         | Alpha-linolenic acid                                 |
| ALT         | Alanine aminotransferase                             |
| AMPK        | 5'-Adenosine monophosphate-activated protein kinase  |
| AST         | Aspartate aminotransferase                           |
| DHA         | Docosahexaenoic acid                                 |
| EPA         | Eicosapentaenoic acid                                |
| FBG         | Fasting blood glucose                                |
| FFA         | Free fatty acids                                     |
| HDL         | High-density lipoprotein cholesterol                 |
| cholesterol |                                                      |
| HFD         | High-fat diet                                        |
| HFHF        | High-fat and high-fructose diet                      |
| IR          | Insulin resistance                                   |
| LDL-c       | Low-density lipoprotein cholesterol                  |
| MAFLD       | Metabolic dysfunction-associated fatty liver disease |
| NAFLD       | Nonalcoholic fatty liver disease                     |
| NF-κB       | Nuclear factor kappa-B                               |
| PPARα       | Peroxisome proliferator-activated receptor α         |
| PPARγ       | Peroxisome proliferator-activated receptor γ         |
| PUFA        | Polyunsaturated fatty acid                           |
| ROS         | Reactive oxygen species                              |
| SCFAs       | Short-chain fatty acids                              |
| SREBP-1     | Sterol regulatory element binding protein-1          |

|       |                             |
|-------|-----------------------------|
| T2DM  | Type 2 diabetes mellitus    |
| TC    | Total cholesterol           |
| TG    | Triglycerides               |
| TNF-α | Tumor necrosis factor-alpha |

## Data Availability Statement

The data from the current study are available from the corresponding author upon a reasonable request.

## Disclosure

All authors read and approved the final version of the manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Author Contributions

M.P. and S.A. wrote the original paper; H.T., S.R.A., and M.E-M. contributed to the conception of the article and provided advice and consultation; M.E-M. and H.T. contributed to the final revision of the manuscript.

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